REMARKS

I. Preliminary Remarks

Upon entry of this amendment, claims 43, 46, 48-50, 53, 54, 58, 59, 61, 62, 65, 67, 70-73, 75, 80-82, 85, 86, 89-92 and 94 are amended herein, new claims 98-99 are added and claim 45 is canceled. Support for new claims 98-99 can be found throughout the specification as filed.

Applicants do not intend these or any other amendments to abandon the subject matter of any claim as originally filed, and reserve the right to pursue such subject matter in this or related applications, including but not limited to parent and continuing applications.

II. The rejection under 35 U.S.C. § 112, first paragraph (written description), should be withdrawn.

The Examiner rejected claims 43-96 under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement.

The Examiner rejected claim 43 as assertedly not being supported by a description of the genus of "inhibitors" recited in claim 43. Claim 43 has been amended to recite the inhibitors recited in claim 45, rendering moot the basis for the rejection.

The Examiner further asserted that the specification fails to disclose a reasonable number of species to support the genus of inhibitors recited in the claims. Applicants disagree. According to the Patent Office's Written Description guidelines, the "essential goal" of the written description requirement is to clearly convey the information that an Applicant has invented the subject matter which is claimed. Logic dictates that the focus of this inquiry is different, depending on what subject matter is being claimed. The fundamental consideration of describing what an Applicant has invented is different in the context of a method of treatment invention involving a newly discovered target than a chemical compound invention.

The present invention is directed to *a method of treatment*, and is based in part on the discovery that inhibition of Flt4 biological activity in vascular endothelial cells, *e.g.*,

by inhibiting ligand-mediated stimulation of Flt4, represents a novel and nonobvious way to treat a disease. The Written Description Guidelines recognize that an Applicant can show possession of the claimed invention by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. (See 66 FR 1104, col. 3.) "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." (66FR 1105, col. 3.) In the case of the presently claimed method, the distinguishing characteristic need not be structural characteristics of compounds, but rather can be functional characteristics of a therapeutic that will be administered and/or steps of identifying patients likely to benefit from the novel treatment approach. (See 66 FR 1106, cols. 1-2, distinguishing structures of products from acts of a process.) Since the claims are directed to a method of treatment by inhibiting a particular target (Flt4 expressed in blood vascular endothelial cells), the claims reasonably convey the invention to persons of ordinary skill and is reasonably commensurate in scope with the teachings of the invention, because it is limited to methods that include administering compositions that inhibit ligand binding to Flt4. These claims will not "encompass" compounds, but rather only *a particular use* of certain compounds known or shown to have a particular biological effect, and this use represents one of the Applicants' contributions to this field.

The Patent Office's "Revised Interim Written Description Guidelines Training Materials" provide two salient examples which illustrate the differences between method and product claims articulated above. In Example 10, a process for producing an isolated polynucleotide via a hybridization experiment is deemed adequately described, even though a claim to a genus of isolated DNAs is not. Also, in Example 18, a process for producing proteins is adequately described in part because no particular nucleic acid is essential to the process. Only a single embodiment was described.

The genus of compounds that are *used* in the methods of the claims is supported in the application by a fair and representative number of exemplary species and subgenuses of compounds, including anti-Flt4 antibodies and fragments thereof; anti-ligand antibodies and fragments thereof; soluble Flt4 fragments that will bind circulating ligand to prevent the ligand from binding Flt4 on cells; ligand fragments that bind but do not stimulate

Flt4; and small molecules. (*See*, e.g., specification at pages 15-16 and 77-78.) Also, the application describes and enables binding assays to determine other compounds having the desired properties.

Moreover, some of the inhibitors recited in the claims are directed to anti-Flt4, anti-VEGF-C and anti-VEGF-D antibodies. The specification provides amino acid sequences for each of Flt4 (SEQ ID NOs: 2, 4), VEGF-C (SEQ ID NO: 21) and VEGF-D (SEQ ID NO: 22). The written description requirement of Section 112 is satisfied where a claimed antibody is defined by its ability to bind a fully characterized antigen. *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004) ("[A]s long as an applicant has disclosed a '*fully characterized* antigen,' either by its structure, formula, chemical name, or physical properties . . . the applicant can then claim an antibody by its binding affinity to that described antigen.").

Some of the inhibitors recited in the claims are directed to a soluble Flt4 fragment or a polypeptide comprising a Flt4 binding fragment of VEGF-C or VEGF-D. As discussed above, the specification teaches a complete cDNA and deduced amino acid sequence of Flt4, which permit one skilled in the art to make any desired fragment of Flt4 using conventional recombinant DNA techniques, and isolate non-human Flt4 orthologs (species variants). The specification teaches the structure of Flt4, including the location of the extracellular (EC) domain that binds a ligand (i.e., VEGF-C or VEGF-D) and the location of several immunoglobulin-like domains within the EC domain. (See, e.g., Figure 2) The specification also teaches working examples of a ligand-binding extracellular domain fragment of Flt4, and chimeric proteins comprising the Flt4 EC domain such as an Flt4-EC-Ig fusion, which would be expected to have increased solubility and serum half-life. (See, e.g., specification at pages 29-36; Examples 14, 25 (Flt4 EC fusion proteins).

Finally, the Examiner asserts that the specification fails to adequately describe the genus of "blood vascular endothelial marker antigens." Applicants disagree. The specification discloses at least six exemplary blood vascular endothelial marker antigens. See, page 15, lines 23-28. Applicants respectfully submit that the specification discloses a representative number of species for the claimed genus.

In view of the foregoing, Applicants respectfully submit that the claims are fully supported by the specification as filed. Accordingly, the rejection should be withdrawn.

III. The rejection under 35 U.S.C. § 112, first paragraph (enablement), should be withdrawn

The Examiner rejected claims 43-96 as assertedly failing to be supported by an enabling specification. The Examiner asserts that the Applicant's disclosure is limited to the anti-Flt4 antibody. Applicants disagree. The specification provides an enabling disclosure for all of the Flt4 inhibitors recited in the claims.

With respect to VEGF-C and -D antibodies and antigen-binding fragments thereof, the specification is enabling because the structure of antibodies is known and one of skill in the art is able to isolate antigen-binding regions of such antibodies using routine methods known in the art. Attached as Exhibit A is an excerpt from a well-known laboratory manual for manipulating antibodies, showing the structure of antibodies, including the variable regions that have long been known to be responsible for antigen specificity. It is well known that the hypervariable regions or "complementarity determining regions" (CDR) comprise the principal portions of an antibody's antigen binding surface. (See Exhibit A at pp. 12, 23.) Reports of scientists isolating antigen binding fragments of antibodies, or selecting CDR regions from non human antibodies and grafting them into human antibody structures are legion, and demonstrate that identification of antigen binding fragments of antibodies does not involve "undue experimentation." Example 29 of the application, which pertains to humanization of antibodies, describes a number of techniques for manipulating antigen-binding fragments of antibodies to make such fragments useful for therapy. The significant guidance provided by the application and by the many decades that scientists have studied immunoglobulins distinguishes the subject matter of the present claims from the subject matter of claims directed to fragments of novel proteins that have not yet been as heavily characterized. Moreover, the identification of VEGF-C or VEGF-D antibodies recited in the claims would not require undue experimentation because the specification teaches a phosphorylation assay that permits the skilled artisan to identify VEGF-C and VEGF-C antibodies that inhibit Flt4 function by routine screening, without epitope mapping.

With respect to Flt4 fragments, the specification is enabling because of its extensive teachings related to Flt4 (discussed above in Section II). The application teaches Flt4 and Flt4 ligands, and thus enables binding assays to screen Flt4 fragments (including smaller Flt4 extracellular domain fragments) for ligand-binding ability. (See, e.g., Example

12 (identification of ligand that binds Flt4 EC); Examples 15-17 (description of VEGF-C and VEGF-D ligands of Flt4). This type of screening protocol is precisely the type of work characterized by the *In re Wands* decision as permissible "routine screening" and not "undue experimentation." For example, the Wands case characterized the entire series of events involving immunizing animals, fusing lymphocytes to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics as a single experiment, and found no undue experimentation. See *In re Wands*, 8 USPQ2d 1400, 1407 (Fed. Cir. 1988). The analogous processes involved in making Flt4 peptide-encoding polynucleotides, expressing the encoded Flt4 fragments, and screening the fragments for activity is merely routine screening, permissible under §112, first paragraph.

While the Examiner admits that the state of the art for an antibody to Flt4 as an inhibitor of Flt4 function is well characterized, he further asserts that other Flt4 inhibitors (i.e., VEGF-C or -D antibodies or antigen binding fragments thereof, and Flt4 fragments) are still under development. The Examiner relies on Karpanen et al., (Am. J. Pathol., 169:708-718, 2006) as allegedly teaching that inhibition of Flt4-function with anti-VEGF-C or -D antibodies remains to be established. A fairer and more accurate characterization of Karpanen is that the only discussion of VEGF-C antibodies pertained to the use of such antibodies to precipitate VEGF-C from conditioned media. See p. 709, column 2 and Figure 1. Thus, the paper proves that VEGF-C antibodies can be made and that they effectively bind VEGF-C. Otherwise,, Karpanen is silent with respect to the effect of anti-VEGF-C and -D antibodies. In fact, Karpanen does not discuss anti-VEGF-D antibodies at all! With respect to soluble VEGFR-3 fragments, Karpanen entirely supports a conclusion that the application is enabling. Specifically, Karapen reported that both a soluble VEGFR-3 ("VEGFR-3-Ig protein") and a VEGFR-3 antibody were capable of inhibiting lymphatic growth in a model that was chosen due to lymphatic hyperplasia. The authors concluded that their data supported the notion that blocking of VEGF-C and –D should be a safe method to inhibit tumor metastasis. Accordingly, to the extent that Karpanen et al. is relevant to the current application, it is relevant because it *supports* a conclusion of enablement.

The Patent Office observes that the Karpanen authors concluded that normal lymphatic vessels are not affected and concluded, from this observation about safety, that inhibition of Flt4 function remains to be established. To the contrary, the study provides proof of efficacy against the neoplastic growth that a medical practitioner would seek to target. The observation that *normal* tissues are not affected would be understood by persons in the field as a *benefit* because side-effects would be reduced. The apparent absence of effects on *normal* tissues would not be construed by persons of ordinary skill as casting doubt ofn efficacy against target neoplastic tissues.

Since the priority date of this application, there have been numerous reports on the functionality of the Flt4 inhibitors recited in the claims. For example, He et al. (J. Natl. Cancer Inst., 94:819-825, 2002 and Cancer Res., 65:4739-4746, 2005; set forth in Exhibit B) reports that adenoviral expression of a Flt4 fragment (i.e., VEGFR-3-Ig) inhibits Flt4 signaling *in vivo*. Lin et al. (Cancer Res., 65:6901-6909, 2005; set forth in Exhibit C) also report that a soluble Flt4 fragment (i.e., sVEGFR-3-Fc) expressed by a recombinant adeno-associated viral vector inhibited Flt4 function (i.e., binding of Flt4 to VEGF-C) both *in vitro* and *in vivo*.

Submitted herewith is a declaration of Dr. Kari Alitalo that was filed in connection with parent application no. 09/169,079, now U.S. Patent No. 6,824,777, (set forth in Exhibit D), which provides scientific evidence directly relevant to the issues raised in the outstanding Office action. For example, the Office action questions whether Flt4 inhibitors other than Flt4 antibodies work as described in the specification. In the declaration, Dr. Alitalo summarizes results of multiple *in vivo* studies providing evidence that compounds that inhibit ligand binding to Flt4 (e.g., soluble Flt4 extracellular domain fragments; anti-Flt4 antibodies) have measurable biological effects *in vivo*, including effects of inhibiting tumor growth in multiple models. The experiments reported in the declaration also demonstrate that an extracellular domain fragment comprising only three of the immunoglobulin-like domains of Flt4 can bind ligands VEGF-C and -D with efficiency comparable to that of full length Flt4. The declaration also demonstrates that antibodies raised against a ligand for Flt4 (i.e., VEGF-D) are effective for blocking ligand interactions with the Flt4 receptor.

Also submitted herewith is a second declaration of Dr. Alitalo that was filed in connection with parent application no. 09/169,079, now U.S. Patent No. 6,824,777, (set forth in Appendix E), which provides further experimental evidence that Flt4 inhibitors demonstrate efficacy for tumor therapy. The second declaration describes studies which revealed that a natural ligand for Flt4, VEGF-C, is overexpresssed in a human lung cancer cell line when compared to a parental cell line with lower metastatic capacity. The study demonstrated that inhibition of the Flt4 signaling pathway with inhibitors according to the present invention can suppress tumor lymphangiogenesis and lymphatic metastasis. Since the metastasis through the lymphatic system correlates with poor prognosis in many cancer patients, this additional data is evidence of efficacy.

Finally, claims directed to VEGF-C and VEGF-D antibodies were recently allowed in U.S. Patent Application Nos. 10/792,461 and 10/161,694, respectively. The '461 and '694 applications both claim priority dates earlier than the present application, which demonstrates that both VEGF-C and VEGF-D antibodies were known in the art prior to the filing date of the present application.

By virtue of the evidence provided in the form of sworn declarations, the rejection alleging lack of enablement should be withdrawn.

IV. The rejections under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Examiner rejected claims 45, 49, 53, 58, 61, 67, 71, 81, 85, 89 and 91 as allegedly being indefinite for use of the phrase "a polypeptide comprising an antigen-binding fragment thereof." In response, claims 45, 53, 61, 67, 71, 81, 85, 89 and 91 have been amended to recite antigen-binding fragment of said anti-Flt4 or anti-VEGF-C or anti-VEGF-D antibody. This non-narrowing amendment renders moot the basis for the rejection. As discussed above in Section III, one of skill in the art is able to isolate antigen-binding regions of such antibodies using routine methods that were known in the art at the time the application was filed. There is no ambiguity understanding what portion of an antibody immunoreacts with its target antigen. Claim 49 is canceled. Claim 58 does not recite the phrase rejected by the Examiner.

The Examiner further rejected claims 43, 49 and 50 as allegedly being vague and indefinite due to the omission of the Flt4 function which is to be inhibited. Applicants traverse. The specification details the functions of Flt4. The specification at pages 11-12 explicitly teach methods of monitoring Flt4 function where it is taught that inhibitors are simply added to the conditioned media containing the Flt4 ligand and if the candidate inhibitors inhibit autophosphorylation, they act as Flt4 signaling inhibitors. At page 12, last paragraph, the application also describes that it is effective to inhibit Flt4 function by inhibiting the binding of an Flt4 ligand protein to Flt4 expressed in cells of an organism. From these and other teachings in the specification, those of skill in the art will readily understand the meaning of the term "Flt4 function" and will be able to tell when a therapeutic agent inhibits it.[1] Flt4 is repeatedly identified in the specification as a tyrosine kinase (specification page 1). By definition, Flt4 and other kinases, function to phosphorylate tyrosine residues. In appropriate contexts, kinases may be phosphorylated themselves (autophosphorylation). As with other receptors, the function of Flt4 is also to bind ligands.

In view of the foregoing, Applicants respectfully request the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

V. The obviousness-type double patenting rejections should be withdrawn.

The Examiner rejected claims 43-46, 49, 51, 52, 54-60, 61-64, 71-76 as allegedly being unpatentable over claims 1-5, 14-49 of U.S. Patent No. 6,824,777. The Examiner asserts that the present invention encompasses all methods of inhibiting Flt4 function in a mammalian organism with a neoplastic disease. Applicants respectfully disagree.

At the outset, it appears that an improper standard of review is being applied to assess double patenting. The double patenting rejections make reference to embodiments in the specification that purportedly contribute to the conclusion of obviousness. The MPEP and the case law from the Patent Office's reviewing court make clear that an obviousness-type double patenting analysis is different from an obviousness analysis. Obviousness-type

[1] In addition to the inhibition of binding and inhibition of phosphorylation at the molecular level, inhibition also will be evident from evidence of inhibition of the downstream effects of Flt4 signaling, which also are characterized in the application.

double patenting analysis only involves a comparison of claims, and not an analysis of whether embodiments in the specification of the issued patent (which in this case is identical to the specification of the pending application) would render claims obvious. See MPEP § 804.

All of the pending claims are directed to methods of inhibiting Flt4 function in a mammalian subject having a neoplastic disorder (or other disorder) ***characterized by expression of Flt4 in the blood vasculature*** (e.g., blood vessels, blood vascular endothelial cells, etc) of the subject. Some of the claims further include a specific method step involving, e.g., screening for a condition characterized by blood vessel expression of Flt4. (See, e.g., claims 53-60, 64-70, 87, and 89-93. The claims of the '777 patent do not recite such a method. To the contrary, claims relating to targeting of blood vascular endothelial cells that were *allowed* during prosecution of the '777 patent, *were canceled prior to issuance* because such claims are directed to a distinct invention, See amendment filed on August 28, 2003 in connection with the application preceding the '777 patent (Copy attached hereto as Exhibit F. See also the certificate of correction canceling claim 7 of the '777 patent.

To the extent that one or more claims of the '777 patent are directed to a genus of methods of inhibiting Flt4 function that may encompass the methods claimed in the present application, the present claims are directed to an unobvious subgenus or species within the genus. For example, claims 43, 49, 53, 61, 65, 71, 81, 85, 89, 91, and those claims dependent thereon, require that the neoplastic disease (or other disorder) is characterized by expression of Flt4 in the blood vasculature (e.g., blood vessels, blood vascular endothelial cells, etc), a particular aspect not claimed in the '777 patent. As such, the pending claims 43, 49, 53, 61, 65, 71, 81, 85, 89, 91, and those claims dependent thereon, are not anticipated by the claims of the '777 patent.

Further, it is axiomatic that an unobvious invention that falls within a prior genus can be patentable when the genus is large and the prior art fails to specifically suggest the species. MPEP § 2144.08 states that "some motivation to select the claimed species or subgenus must be taught by the prior art," citing *In re Deuel*, 51 F3d. 1552, 34 USPQ2d 1210 (Fed. Circ., 1995). The present claims are an unobvious subgenus that is neither disclosed nor suggested by any broad methods that are claimed in the '777 patent.

Moreover, claims 46, 50, 54, 62, 72, 73, 78, 82, 86, 90, 92, and those claims dependent thereon, require that the inhibitor for use in the claim-recited methods comprise a bispecific antibody that specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen. Such a bispecific antibody is not recited in any of the claims in the '777 patent. As such, claims 46, 50, 54, 62, 72, 73, 78, 82, 86, 90, 92, and those claims dependent thereon, are not anticipated by the claims of the '777 patent.

As such, the claims of the present invention are patentably distinct from claims of the '777 patent, and the double patenting rejection should be withdrawn.

VI. Conclusion

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

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